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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/046,542	01/16/2002	Wilfred Arthur Jefferies	7685-41	3450

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LANG MICHENER
BCE PLACE, P.O. BOX 747
SUITE 2500, 181 BAY STREET
TORONTO, ON M5J 2T7
CANADA

EXAMINER

WEHBE, ANNE MARIE SABRINA

ART UNIT PAPER NUMBER

1633

DATE MAILED: 06/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/046,542

Applicant(s)

JEFFERIES ET AL.

Examiner

Anne Marie S. Wehbe

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 May 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3,7,8,14 and 17-30 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 3, 7-8, 14, and 17-30 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date: _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date: _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/15/06 has been entered. Applicant's amendment and response received concurrently with the RCE has also been entered. Claims 2, 4-6, 9-13, and 15-16 are canceled, and new claims 21-30 have been added. Claims 1, 3, 7-8, 14, and 17-30 are currently under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Double Patenting

The rejection of previously pending claims 1, 4-5, 7, 9, and 14-19 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,361,770 B1 (3/26/02), hereafter referred to as the '770 patent, is withdrawn over currently pending claims 1, 7, 14 and 17-19, claims 4-5, 9, and 15-16 having been canceled, and maintained over new claims 21-24, and 26-29.

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The rejection over previously pending claims 1, 7, 14, and 17-19 is due to the amendment of claim 1 to recite that the method is for enhancing an immune response to a viral antigen and that the target cell expresses a viral antigen.

The rejection of record applies to new claims 21-24, and 26-29 as the new claims recite methods of enhancing an immune response to a tumor antigen, where the target cell is a tumor cell. As set forth in the previous office actions, claims 1-10 of the '770 patent represent a species of the instant broader claims. It is well established that a species of a claimed invention renders the genus obvious. *In re Schaumann* , 572 F.2d 312, 197 USPQ 5 (CCPA 1978). The claims of the '770 patent are limited to an *ex vivo* method of augmenting the immune response to a tumor by introducing a nucleic acid encoding TAP-1 into a tumor cell *ex vivo* and introducing the tumor cell into the mammal (claims 1-6), and methods of augmenting the immune response to a tumor by directly introducing a vaccinia virus encoding TAP-1 into a tumor (claims 7-10). The instant new claims broadly read on either method. Thus, as a species of the instant broader claims, claims 1-10 of the '770 patent render the instant claims obvious.

The applicant's response does not specifically address this rejection. Previous responses have indicated that the applicant plans to file a terminal disclaimer upon indication of allowable claims. However, since no arguments traversing the grounds of rejection have been presented, and a terminal disclaimer has not been filed, the rejection of record stands.

Claim Rejections - 35 USC 112

The rejection of previously pending claims 1, 3-12, and 14-20 under 35 U.S.C. 112, first

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paragraph, for scope of enablement is maintained over currently pending claims 1, 3, 7-8, 14, and 17-30, claims 4-6, 9-13, and 15-16 having been canceled. . Applicant's amendments and arguments, the declaration under 37 CFR. 1.132 by Dr. Jefferies, and the Ahn et al., Lou et al., and Shankaran et al. references submitted as evidence with the response have all been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

Please note that as claim 10, which recited the limitation of genes inducible by tapasin, has been canceled, the grounds for lack of enablement for genes inducible by tapasin is withdrawn.

The following scope of enablement is identified: 1) methods of augmenting a CTL response in a mammal to tumor cells expressing low or nondetectable levels of peptide/MHC class I complexes on the cell surface comprising ex-vivo introduction of a nucleic acid encoding TAP-1 into the tumor cells followed by introduction of the tumor cell into the mammal, 2) methods of augmenting a CTL response in a mammal to a tumor cell expressing low or nondetectable levels of peptide/MHC class I on the cell surface comprising introducing a viral vector encoding TAP-1 into or near the tumor cell, and 3) in-vitro methods of enhancing a CTL response to VSV antigens in a cell expressing low or nondetectable levels of peptide/MHC I on the cell surface comprising, introducing into said cell a nucleic acid comprising a sequence encoding TAP-1 or TAP-2.

The applicant argues that claims 1, 3, 7-8, 14, and 17-20 have been amended to recite methods of enhancing an immune response to a viral antigen and that the specification provides an enabling disclosure for enhancing the immune response to viral antigens by transfecting a

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target cell expressing the viral antigen with either TAP-1 or TAP-2. The applicant argues that the specification in example 12 demonstrates that the transfection of either TAP-1 or TAP-2 alone into CMT cells which do not express detectable TAP-1 or TAP-2 is sufficient to increase presentation of VSV peptides and increases CTL responses *in vitro*, and that Figure 18 shows increased CTL responses to Influenza antigens in cells transfected with TAP-1. Regarding Influenza antigens, the applicant also refers to the Declaration by Dr. Jeffries under 37 CFR 1.132. This declaration is a copy of the declaration first filed in the parent application 08/817,731 on 3/12/99.

In response, the scope of enablement identified above already states that the specification is enabling for *in vitro* methods of enhancing a CTL response to VSV antigens in a cell expressing low or nondetectable levels of peptide/MHC I on the cell surface comprising, introducing into said cell a nucleic acid comprising a sequence encoding TAP-1 or TAP-2. However, applicant's declaratory evidence and arguments do not overcome the lack of enablement in the specification for the enhanced presentation of any and all viral peptides in the context of MHC class I on the surface of any target cells which have been transfected with TAP-1 or TAP-2. As discussed in the previous office action, the specification demonstrates that CMT.64 transfected with TAP-1 and infected with Influenza are not lysed by Influenza specific CTL suggesting that TAP-1 is not sufficient to allow processing and presentation of endogenous Influenza peptides in CMT.64 cells (specification, page 46, lines 27-30, Figure 17). Please note in particular that the specification on page 46, lines 27-28, specifically states, "Influenza virus infected cells were found to be efficiently recognized only if both rat TAP genes are present (Figures 16-18)". Thus, the applicant's analysis of their own experiments concludes that both

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TAP-1 and TAP-2 expression is required for efficient presentation of Influenza peptides in order to stimulate CTL responses. The applicant's declaratory evidence, in particular Figure 3, appears to refute the data presented in the specification by showing a graph depicting the lysis of CMT1-4 or CMT2-10 infected with Influenza virus by Influenza specific CTL. The applicant's do not explain this discrepancy or disclose changes to the experimental protocol that resulted in the observation of lysis in the newly presented data. Further, as noted above, the specification itself concludes that both TAP molecules are required to present Influenza peptides in a target cell. Thus, in view of the conflicting nature of the data presented in the applicant's declaration as compared to that disclosed in the specification, and the teachings of the specification, the applicant's declaratory evidence would not convince the skilled artisan that CMT.64 cells transfected with TAP-1 alone actually enhance the presentation of Influenza peptides in the context of MHC class I on the cell surface.

Further, as discussed in the prior office action, the applicant's working example using HSV infected CMT.64 cells shows that HSV peptides are processed and presented independent of TAP-1 and TAP-2 as untransfected CMT.64 cells infected with HSV are lysed with equal efficiency as TAP-1 transfected CMT.64 (specification, page 47, lines 3-5 and Figure 19). The applicant's response further confirms these results as the paper by Ahn et al., submitted as evidence with applicant's response, shows that HSV itself inhibits TAP-mediated translocation of HSV peptides across the endoplasmic reticulum.

Thus, viewed as a whole, the applicant's working examples demonstrate that of the viral antigens tested, only VSV peptides are capable of being processed, presented, and expressed on the cell surface of CMT.64 cells transfected with TAP-1 or TAP-2 in the context of MHC class I,

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and of being recognized by viral specific CTL. Therefore, the scope of enablement limiting the applicant's methods to VSV viral antigens is maintained.

It is noted that while applicant's declaration further provides experiments involving the recognition and lysis of TAP-1 or TAP-2 transfected CMT.64 cells, which express class I molecules of the H-2^b haplotype, by anti-H-2^b alloreactive H-2^d CTL, these experiments are not relevant to the enablement of the claims as amended as the claims are not limited to enhancing immune responses against viral antigens or tumor antigens.

The applicant further argues that the specification is enabling for the delivery of nucleic acids encoding a TAP molecule to a target cell *in vivo* using vectors other than vaccinia virus and any route of delivery. In support of their arguments, the applicant has provided publications by Lou et al. and Shankaran et al. In response, it is first noted that the Shankaran et al. reference provided with the response is entitled "IFN γ and lymphocytes prevent primary tumor development and shape tumor immunogenicity". Contrary to applicant's description of this reference, the Shankaran publication provided does not disclose intraperitoneal TAP-1 administration as it is directed to the transfection of tumor cells *in vitro*, see page 1110. Thus, Shankaran does not provide any evidence for *in vivo* administration of any type of vector encoding TAP-1. Regarding the teachings of the Lou et al. reference, this reference demonstrates that an adenoviral vector encoding TAP-1 can be used to effectively express TAP-1 in tumors cells *in vivo* when delivered locally to a tumor. Note that as Lou et al. teaches the intraperitoneal administration of the virus vector to a mammal with intraperitoneal tumors, the delivery is not systemic or distal since the tumor cells to be transduced as in the vicinity of the injection. Based on the evidence provided by Lou et al., the scope of enablement has been broadened to include

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the *in vivo* administration of a viral vector encoding TAP-1 into or near a tumor. However, applicant's supplemental evidence does not address the lack of enablement for targeted transfection of virally injected cells or tumor cells *in vivo* by administering any nucleic acid encoding TAP-1 by any route of administration. The previous office action cited the teachings of Verma et al, Miller et al., and Orkin et al., to demonstrate that at the time of filing, the art considered the targeted *in vivo* delivery of recombinant vectors, and the expression of therapeutic levels of the encoded transgenes in the target cells as unpredictable. Further, as stated in previous office actions, the specification does not teach strategies to target vector to tumor cells *in vivo* other than by direct, localized injection of the vector into the tumor itself. Regarding virally infected cells, the specification does not provide any strategy or working examples for targeted transfection of any type of virally infected cell in a mammal. As discussed above, the Lou et al. and Shankaran references relied upon by the applicants do not overcome the evidence of record for the unpredictability of targeting either virally infected cells or tumors *in vivo* by administering viral vectors or plasmids systemically or to sites distal from the site of the virally infected cells or tumors.

Thus, based on the unpredictable effects of gene delivery using both viral and non-viral vectors as taught by the art at the time of filing, and the lack of guidance provided by the specification for the use of any and all vectors and routes of *in vivo* vector delivery other than the direct administration of viral vectors encoding TAP-1 to or near the tumor site, it would have required undue experimentation for the skilled artisan to practice the instant invention as claimed. The applicant's argument that one skilled in the art could readily administer TAP

molecules using other vectors and modes of administration is contradicted by the teachings of Verma et al., Miller et al., and Orkin et al.

Thus, for the reasons discussed in detail above, the rejection of record is maintained.

The rejection of previously pending claim 10 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is withdrawn in view of applicant's cancellation of the claim.

Claim Rejections - 35 USC 102

The rejection of previously pending claims 1-5, 7-8, 16, and 19 under 35 U.S.C. 102(b) as being anticipated by Spies et al. (1992) Nature, Vol. 355, 644-646, is maintained over currently pending claims 1, 3, 7-8, and 19, claims 2, 4-5, and 16 having been canceled.. Applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed below.

The applicant states that Spies increased viral antigen presentation by transfecting mutant .134 cell which is missing the TAP-1 gene, but has the TAP-2 gene, with the TAP-1 gene. The applicant argues that in contrast to Spies, the applicant has shown that TAP-1 or TAP-2 alone is able to enhance the processing and presentation of viral antigens in CMT.64 cells that lack both

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TAP-1 and TAP-2. In response, applicant is arguing limitations from the specification that are not in the claims as written. The applicant is reminded that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Claims 1, 3, 7-8, and 19 place no limitation on the characteristics of the target cell in terms of TAP-1 and/or TAP-2 expression. The method simply recites that TAP-1 or TAP-2 expression is increased in the target cell transformed with the vector encoding TAP-1 or TAP-2. Thus, applicant's argument is not persuasive as the claims are not limited to target cells that do not express either TAP-2 or TAP-1.

The rejection of previously pending claims 1-4, 6-8, 16, and 19 under 35 U.S.C. 102(b) as being anticipated by Powis et al. (1991) *Nature*, Vol. 354, 528-531, is maintained over currently pending claims 1, 3, 7-8, and 19, claims 2, 4, 6, and 16 having been canceled.. Applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed below.

The applicant states that Powis et al. increased viral antigen presentation by transfecting mutant RMA-S cell which is missing the TAP-2 gene, but has the TAP-1 gene, with the TAP-2 gene. The applicant argues that in contrast to Powis, the applicant has shown that TAP-1 or TAP-2 alone is able to enhance the processing and presentation of viral antigens in CMT.64 cells that lack both TAP-1 and TAP-2. In response, applicant is arguing limitations from the specification that are not in the claims as written. The applicant is reminded that although the claims are interpreted in light of the specification, limitations from the specification are not read into the

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claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Claims 1, 3, 7-8, and 19 place no limitation on the characteristics of the target cell in terms of TAP-1 and/or TAP-2 expression. The method simply recites that TAP-1 or TAP-2 expression is increased in the target cell transformed with the vector encoding TAP-1 or TAP-2. Thus, applicant's argument is not persuasive as the claims are not limited to target cells that do not express either TAP-2 or TAP-1.

No claims are allowed.

This is an RCE of applicant's earlier Application No. 10/046,542. All claims, including new claims 21-30 are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however,

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event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197.

Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER

